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MEMORANDUM

TO: Barry Cortez
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: February 18, 2000

SUBJECT: OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT'S FINDINGS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT TOXIC AIR CONTAMINANT DOCUMENT FOR METHYL PARATHION

Pursuant to Food and Agricultural Code Sections 14022 and 14023, please find attached our findings on the Department of Pesticide Regulation's draft toxic air contaminant document for methyl parathion. If you have any questions, please contact me at (510) 622-3200.

Attachment

cc: Joan E. Denton, Ph.D.
Director
Office of Environmental Health Hazard Assessment

Val F. Siebal
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Bill Lockett
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Office of Environmental Health Hazard Assessment (OEHHA) Findings on the Department of Pesticide Regulation (DPR) Draft Toxic Air Contaminant (TAC) Document for Methyl Parathion

June 15, 1999

Pursuant to Food and Agricultural Code sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) of Cal/EPA provided consultation to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of the active ingredient methyl parathion. Furthermore, OEHHA has reviewed the draft documents on the evaluation of the human health risks associated with the potential exposure to methyl parathion for the purposes of considering the identification of methyl parathion as a Toxic Air Contaminant (TAC). As part of its statutory responsibility, OEHHA has prepared these findings on the health effects of methyl parathion which are to be included as part of the DPR report.

Environmental Fate and Exposure

1. The evaluation of methyl parathion as a TAC by DPR was based on its airborne concentrations in ambient air. The most relevant monitoring study attempting to characterize the ambient air exposure was the study conducted in Colusa and Sutter counties during methyl parathion application season to rice (Seiber *et al.*, 1987). Rural ambient air levels of methyl parathion monitored at four locations ranged from non-detectable (detection limits 0.2 ng/m^3 or 0.02 ppt) to 34.7 ng/m^3 (3.2 ppt), corrected for trapping efficiency and storage recovery. The mean levels for the sampling locations ranged from 0.3 ng/m^3 (0.03 ppt) to 8.4 ng/m^3 (0.78 ppt). The highest levels of methyl parathion were detected in Colusa county.

2. The most relevant monitoring studies attempting to characterize the application site air exposures were conducted in Sutter (ARB, 1989) and in Glenn counties (Seiber and McChesney, 1987). Application site air levels of methyl parathion ranged from 51 ng/m^3 (4.7 ppt) 48 hours after the application to 1,030 ng/m^3 (96.0 ppt) one hour after the application at 17 yards from the edge of the treated field.

3. Quantitative assessment of human exposure appropriately included both airborne methyl parathion and its main and more toxic environmental breakdown product paraoxon. Inhalation, ingestion and dermal contact are all significant sources of human exposure to methyl parathion.

4. Oral absorption of methyl parathion was assumed to be 100%, a value that is consistent with the scientific data that indicate absorption from the gastrointestinal tract is both rapid and complete.

5. Inhalation exposure estimates were based on the assumption that airborne methyl parathion was in the particulate phase and was 100% absorbed.

6. Specific data for dermal absorption of methyl parathion in humans are not available. Data for dermal absorption for ethyl parathion in humans are available; one study reported a dermal absorption rate of 10%, another estimated a range of 10 to 30% absorption.

Health Effects

General

7. Absorbed methyl parathion is metabolically activated to methyl paraoxon. Detoxification involved dealkylation and dearylation, and elimination as *p*-nitrophenol in the urine.

8. Methyl paraoxon inhibits ChE by binding to its active site. Inhibition of plasma, red blood cell (RBC), and brain cholinesterase (ChE) are well documented. The consequences of accumulation of the neurotransmitter acetylcholine (ACh) at nerve junctions are manifested in adverse neurological signs and symptoms of both the peripheral and central nervous systems.

9. Age-specific and individual differential sensitivity to methyl parathion toxicity have been demonstrated. Young rats can be approximately 10-fold more sensitive than the adults to the acute toxicity of methyl parathion. The activities of paraoxonase, the enzyme that breaks down methyl paraoxon, can vary by more than 60-fold in humans, potentially resulting in significant variation in interindividual sensitivity.

Humans

10. Acute (one to several days) and subchronic (several days to 3 months) exposures to methyl parathion result in measurable plasma and RBC ChE inhibition. The inhibition of brain ChE is evident in the cholinergic effects. Cholinergic effects reported in human acute poisoning cases are those typical of cholinergic over-stimulation, such as salivation, lacrimation, miosis, defecation, urination, headache, dizziness, labored breathing, twitching, convulsions and death.

11. Methyl parathion acute poisoning may also result in intermediate syndrome (IMS) which typically appears 1 to 4 days after successful treatments of cholinergic crisis. IMS includes myopathy, respiratory paralysis, nerve palsies, and muscle weaknesses.

Animal

12. Acute (one to several days) and subchronic (14 days to 3 months) exposures to methyl parathion result in plasma, RBC, and brain ChE inhibition. Cholinergic effects commonly reported in animals are lacrimation, salivation, shivering, muscle fasciculation, labored breathing, and other neurological effects. Neurobehavioral and neurohistopathological changes have also been reported.

13. Chronic (beyond 1 year) exposure to methyl parathion results in ChE inhibition (plasma, RBC, brain), tremors, alopecia, body weight changes, paralysis, as well as myelin degeneration of nerves.

14. Data from chronic studies and cancer bioassays appear to indicate that development of a cancer potency value for methyl parathion is not appropriate. However, it should not be overlooked that the overall database indicates that methyl parathion has genotoxic potential.

15. Methyl parathion decreases the survival and body weight of rat pups in 2- and 3-generational reproductive toxicity studies and can cause male and female reproductive toxicities.

16. The developmental effects of methyl parathion include lower fetal body weight, increased resorption, reduced pup survival, and abnormalities and variations in fetal ossification in rats and rabbits. Neurobehavioral changes can result from *in utero* exposures.

Potency and Range of Risk to Humans

17. Assessment of risk from potential exposures to methyl parathion in humans was based on its potential for noncarcinogenic effects, expressed in terms of margin of exposures (MOEs). In general, OEHHA supports the selection of toxicological studies selected by DPR for use in its methyl parathion risk assessment.

18. MOEs for acute ambient air exposures ranged from 390 to 4800 depending on the study used for assessment. When based on a rat study, the MOEs were at least 390 with severe cholinesterase inhibition (plasma, RBC, brain) and nerve demyelination observed at the LOEL of 7.5 mg/kg-day and some indication of demyelination at the NOEL of 0.025 mg/kg-day. The MOEs of 4800 or greater were calculated from a human study with a NOEL of 0.31 mg/kg-day for plasma and RBC cholinesterase inhibition observed at the LOEL of 0.34 mg/kg-day.

19. MOEs for the ambient seasonal exposures ranged from 150 to 16,000 depending on the study used for assessment. When based on a dog study, the MOEs were at least 150 with plasma cholinesterase inhibition observed at a LOEL of 0.03 mg/kg-day and an estimated NOEL of 0.003 mg/kg-day. When based on a human study the MOEs were 16,000 or greater. In the human study (the same study used for the acute MOE estimation) the NOEL was 0.31 mg/kg-day for plasma and RBC cholinesterase inhibition observed at the LOEL of 0.34 mg/kg-day.

20. MOEs for the ambient chronic exposures ranged from 670 to 1,300 depending on the study used for assessment. When based on a two-year study in rats the MOEs were at least 670 with the LOEL of 0.09 mg/kg-day for RBC cholinesterase inhibition and an estimated NOEL of 0.01 mg/kg-day. In three other chronic studies (one in mice and two in rats) the established NOEL was 0.02 mg/kg-day. This NOEL was based on brain cholinesterase inhibition in mice and nerve demyelination, abnormal gait, and hematological alterations observed in two rat studies. MOEs calculated from the latter were 1,300 or greater.

21. For potential exposures at the site of application (17 yards from the field), MOEs ranged from as low as 20 up to 250. The first estimate was based on cholinesterase inhibition (plasma, RBC, brain) and nerve demyelination in rats at the LOEL of 7.5 mg/kg-day and

some indication of demyelination at the NOEL of 0.025 mg/kg-day. The second estimate of 250 was based on a human study (discussed above) with a NOEL of 0.31 mg/kg-day and a LOEL of 0.34 mg/kg-day for cholinesterase inhibition in plasma.

22. The DPR Report establishes a Toxicity Equivalency Factor (TEF) of 10 for methyl paraoxon, relative to methyl parathion toxicity. This factor was derived by rounding the ratio of acute methyl paraoxon toxicity to acute methyl parathion toxicity (4.5 – 8.2) derived from rat and mouse acute toxicity studies up to 10.

23. DPR has calculated Reference Concentrations (RCs) for acute, seasonal and chronic exposures to methyl parathion (listed in Table 1). These values are generally similar to OEHHA Reference Exposure Levels (RELs), with the exception that the concentrations use 24-hour exposure assumptions; OEHHA acute RELs are based on 1-hour exposures. These RCs are calculated from mouse (chronic), rat (acute, seasonal, chronic), dog (seasonal) and human (acute, seasonal) data. The RC calculations use default breathing rate (16.7 m^3/day) and body weight (22.6 kg) parameters for a 6-year old child. RCs were developed from each study using each of two exposure assumptions: 1) exposure is to methyl parathion only; 2) exposure is to methyl parathion plus methyl paraoxon at 25% of the methyl parathion concentration. The second exposure assumption incorporates a TEF of 10 for methyl paraoxon as described above. OEHHA generally supports the methodology used in making these determinations.

Table 1: Reference Concentrations (RCs) for acute, seasonal and chronic methyl parathion 24-hour exposures.

Species	NOEL (mg/kg-day)	Reference Concentration (RC) ($\mu g/m^3$)	
		MP only	MP + MPoxon
Acute Exposures			
human	0.31	40	12
rat	0.025	0.34	0.1
Seasonal Exposures			
human	0.31	40	12
dog	0.003	0.04	0.01
rat	0.02	0.3	0.08
Chronic Exposures			
rat	0.01	0.14	0.04
mouse/rat	0.02	0.3	0.08

MP = methyl parathion; MPoxon = methyl paraoxon.

Uncertainties and Other Relevant Findings

24. The health risk assessment of methyl parathion presented in the DPR report is based only on inhalation exposure from the air. Methyl parathion present in the air can also be absorbed following ingestion or dermal contact as a result of wet (fog) and dry deposition of the pesticide on vegetation. These potential exposures to methyl parathion from non-inhalation

routes were not quantified and added to the risk estimates for inhalation exposure in the draft report.

25. The scientific data summarized in the draft methyl parathion risk assessment support the finding that there is age-related sensitivity which is greater for young animals including those exposed pre- and post-natally. Age-related sensitivity was seen in acute rat toxicity studies designed to determine LD_{50} and ED_{50} for plasma and brain ChE inhibition and in developmental and reproductive toxicity studies (Section VI.B.3, XI and XII and Table 1 in part C (Human Health Assessment) of the DPR evaluation). The increase in sensitivity in young animals might be as high as 10-fold.

26. Exposure to airborne methyl parathion contributes to the overall risk of cholinesterase (ChE) inhibition from all organophosphate pesticides (OPs) present in the air. The combined risk for ChE inhibition due to cumulative airborne OP exposure was not assessed in the draft report nor is it currently known. Therefore, the contribution of methyl parathion to the total risk of OP activity in inhibiting ChE cannot be determined from the draft report. OEHHA acknowledges that methodologies to assess cumulative risks from exposure to chemicals with a common mechanism of action are not yet widely accepted in the scientific community.

27. Methyl parathion may have disruptive effects on human endocrine functions. Signs of its interference with endocrine systems have been shown in aquatic organisms (including fish), birds and rats. Observed effects were developmental changes (aquatic species, birds and rats), changes in carbohydrate metabolism (prawns, fish, snails, birds, rats) changes in thyroid (fish) and adrenal function (birds) and immunotoxicity (rats).

28. Because of the uncertainties such as the magnitude of potential exposure to methyl parathion from non-inhalation routes, degree of age-related sensitivity, contribution of methyl parathion to the overall risk of ChE inhibition and potential for disruptive effects on endocrine functions, OEHHA finds that higher exposure and risk estimates could occur in certain situations. In the calculation of the MOE, the application of modifying factors to account for the uncertainties and increased sensitivity to children would appear to still result in an adequate MOE for most of the exposure scenarios evaluated by DPR. The only exception would be the exposures at the application site (17 to 20 yards from the field), where the MOE would be 25 (previously 250) based on the human NOEL and 8 to 18 (previously 80 to 180) based on the estimated NOEL in rats. RCs calculated with an additional modifying factor of 10 would be consequently 10 times lower than the values presented in item 23, under "Potency and Range of Risk to Humans". Additionally, as noted in item 9 under "Health Effects", paraoxonase activity (the enzyme that breaks down methyl paraoxon), can vary by more than 60-fold in humans, potentially resulting in significant variation in interindividual sensitivity. This indicates that use of a 10-fold interindividual uncertainty factor may result in an underestimation of noncancer toxicity risk.